II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 69, 91-98, 100, and 114-126 were pending in the case at the time of the Office Action. Claims 69, 91, 93, 98, 115, 119-120, and 122-126 have been amended in the Amendment set forth herein without prejudice or disclaimer. Detail regarding the claim amendments is set forth below. Claims 94, 100, 114, and 118 have been canceled without prejudice or disclaimer. New claims 135-137 have been added. Thus, claims 69, 91-93, 95-98, 115-117, 119-126, and 135-137 are currently pending and presented for reconsideration.

B. Interview Summary

Applicants received an Interview Summary from the Examiner that was mailed on May 1, 2009 concerning the telephonic interview of April 30, 2009. The interview included Examiner McKane, David Parker, Dr. Issam Raad, Matt Browning, Andrew Dennis, and Monica De La Paz. The purpose of the telephonic interview was to discuss proposed claim amendments and the final Office Action dated January 23, 2009 in the present application, and proposed claim amendments and the pending non-final Office Action in the related divisional application, U.S.S.N. 11/875,699.

Applicants do not entirely agree with the Interview Summary set forth by the Examiner. The Interview Summary appears to suggest that the Examiner cautioned during the interview that the instant specification "does not appear to support a showing of unexpected results for the combination of GV and CHX against *MRSA* and *C. Parap.* for a polyurethane device" and that the specification "does not appear to support a showing of unexpected results for the use of brilliant green with chlorhexidine." Interview Summary, last page. However, Applicants have no recollection about the Examiner opining that the specification failed to support a showing of surprising and unexpected results during the interview. Applicants disagree that the specification

fails to support a showing of unexpected results for the scope of the claimed invention, and respond in the discussion below concerning surprising and unexpected results.

The Examiner also indicates in the Interview Summary that "recent case law would seem to suggest that secondary considerations do not always overcome a showing of obviousness." Interview Summary, last page. In particular, the Examiner cited *Agrizap v. Woodstream Corp.*, 520 F.3d 1337 (Fed. Cir. 2008) as supporting her position. Applicants disagree with the Examiner's interpretation of *Agrizap v. Woodstream Corp.* A detailed discussion concerning *Agrizap v. Woodstream Corp.* and other case law concerning obviousness and surprising and unexpected results is discussed in detail below.

C. Claim Amendments

As noted above, claims 69, 91, 98, 115, 119-120, and 122-126 have been amended in the Amendment set forth herein without prejudice or disclaimer. The amendments do not involve entry of new subject matter into the claims but instead narrow the scope of the claims. The amendment is made for the purpose of expediting prosecution of commercially valuable subject matter. Applicants herein specifically reserve the right to prosecute the claims as written prior to entry of the amendment set forth herein in a continuation application, a divisional application, or the present application.

Regarding the amendments, independent claim 1 has been amended to pertain to a method for disinfecting and/or sterilizing a floor, a table-top, a counter-top, hospital equipment, a wheel chair, or a medical device comprising applying a composition consisting essentially of chlorhexidine and a dye selected from the group consisting of gentian violet and brilliant green to the floor, table-top, counter-top, hospital equipment, wheel chair, or medical device, wherein the molar ratio of chlorhexidine:dye in the composition is 1:1 to 25:1. Independent claim 98 has

been amended to pertain to a method for disinfecting and/or sterilizing a floor, a table-top, a counter-top, hospital equipment, a wheel chair, or a medical device comprising applying a composition consisting essentially of chlorhexidine and brilliant green to the floor, table-top, counter-top, hospital equipment, wheel chair, or medical device, wherein the molar ratio of chlorhexidine:brilliant green in the composition is 1:1 to 25:1. Support for the amendment to the claims can be found generally throughout the specification, such as in the claims as originally filed.

It is noted that the claims have been amended to recite that the composition which is applied "consists essentially of" chlorhexidine and a dye that is gentian violet or brilliant green. The transitional phrase "consisting essentially of" is defines the scope of the claim with respect to what unrecited additional components are excluded from the scope of the claim. *MPEP* §2111.03. It is well-settled that the phrase 'consisting essentially of' "limits the scope of the claim to the specified materials 'and those that do not materially affect the basic and novel characteristic(s)' of the claimed invention." *MPEP* § 2111.03 (quoting *In re Herz*, 537 F.2d 549 (CCPA 1976) (emphasis in original); see also *Ex Part Davis*, 80 USPQ 448, 449-50 (Pat. Off. Bd. App. 1948) (A "consisting essentially of" claim occupies a middle ground between closed claims that are written in a "consisting of" format and fully open claims that are drafted in a "comprising" format). It is well-settled that by using the term "consisting essentially of," the drafter signals that the invention necessarily includes the listed ingredients and is open to unlisted ingredients that do not materially affect the basic and novel properties of the invention." *PPG Indus. V. Guardian Indus. Corp.*, 156 F.3d 1351 (Fed. Cir. 1988). Thus, a composition that consists essentially of chlorhexidine and a dye that is gentian violet or brilliant green necessarily

includes chlorhexidine and a dye that is gentian violet or chlorhexidine and is open to unlisted ingredients that do not materially affect the basic and novel properties of the composition.

Non-limiting examples of unlisted ingredients that do not materially affect the basic and novel properties of the invention include solvents as set forth in the example section of the instant specification. A non-limiting example of an ingredient that would affect the basic and novel properties of the invention is a chelator. See Table 11 on page 26 of the specification. More particularly, Table 11 on page 26 of the instant specification demonstrates that silicone catheters coated with a composition that includes gentian violet in combination with a chelator (trisodium n-(2-hydroxyethyl)ethylenediaminetriacetate; [GV†HEDTA]) showed smaller zones of inhibition and were thus less effective against *MRSA* and *C. Paralosilosis.* than Gendine (gentian violet and chlorhexidine) as set forth in table 4.

D. The Claims are Not Obvious Under 35 U.S.C. §103(a)

1. Claims 69, 91-96, 114-119, 121, 122, and 124-126 Are Not Unpatentable Based on Luthra in View of Perelin

Claims 69, 91-96, 114-119, 121, 122, and 124-126 are rejected under 35 U.S.C. §103(a) as being unpatentable over Luthra *et al.* (WO 00/65915; hereinafter "Luthra") in view of Pelerin (U.S. 2002/0009693; hereinafter "Pelerin").

Luthra is a PCT application which concerns polymeric materials that incorporates an infection resistant biguanide such as chlorhexidine or polynexanide pendant to the polymer chain. *See, e.g.*, abstract. The biguanide is *chemically linked* to the polymer through secondary nitrogen atoms of the biguanide. *See* abstract. Luthra teaches that "the biguanide can be incorporated as a pendant group into a polymer which is then made onto or coated on to an article, or the biguanide can be chemically linked to polymer already on an article, or the

biguanide can be bound to polymer on an article through an intermediate non-polymeric compound." Page 7, lines 4-9. Luthra discloses that "[s]uitable medical devices to which the invention may be applied include catheters, blood bags, dialysis or other membranes, surgical gloves, surgical instruments, vascular grafts, stents, contact lenses and intra-ocular lenses, contact lens cases, bottles, diagnostic apparatus, oxygenators, heart valves, and pumps." Page 7, lines 26-30.

Pelerin is a U.S. patent application publication which concerns a dental restoration solutions for root or dentinal tubule treatment that include an orally compatible solvent and a chelating agent at a pH of between 1.2 and 4. *See, e.g.,* Abstract and claim 1. Pelerin indicates that a dye may be "optionally present to identify a tooth region contacted with the inventive solution." Para [0012].

The Examiner argues that one of ordinary skill in the art would be motivated to practice the claimed methods because one of ordinary skill in the art would include an indicator dye of Pelerin (such as gentian violet) in a composition to indicate where the composition of Luthra was applied. Applicants respectfully traverse.

a. No *Prima facie* Case of Obviousness Has Been Set Forth

(1) The Examiner's Characterization of Luthra is Flawed Because it Overlooks Key Aspects of the Technology

The Examiner argues that "Luthra *et al.* teaches a method of disinfecting a medical device by applying a composition containing chlorhexidine thereto." Office Action, page 2. However, Luthra does not teach coating of medical devices with chlorhexidine per se, but instead teaches coating of medical devices with polymers chemically modified to include a covalently attached moiety that is derived from a biguanide such as chlorhexidine. In particular, Luthra

concerns "chemically modified infection resistant materials [that] are produced by the chemical modification of infection resistant biguanide compounds to produce polymers that can be blended into the bulk of other polymers, be used as coatings, or be chemically attached to the surface of a medical device." Page 4, lines 7-10. Luthra teaches that the chemically modified infection control material is "a polymeric material incorporating an infection resistant biguanide compound pendant to the polymer chain, being chemically bound thereto through some but not all of the amine nitrogen atoms...." Page 6, lines 11-13. Luthra further indicates that a medical device "may be formed from or coated with the polymeric material incorporating the infection resistant biguanide compound, or the medical device may first be formed from or coated with polymeric material which is thereafter chemically bound to some but not all of the nitrogen atoms of the infection resistant biguanide compound, or the medical device may first be formed from or coated with polymeric material which is thereafter chemically bound to the residuum of a non-polymeric compound that has been bound to some but not all of the nitrogen atoms of the infection resistant biguanide compound. Paragraph bridging pages 6-7. The end result is that the medical device is coated with a polymer that is chemically modified to include bound biguanide. The distinction is important, as discussed in greater detail below. The Examiner is reminded that the instant claims are not composition claims but method claims that include the limitation of applying a composition consisting essentially of chlorhexidine and a dye that is gentian violet or brilliant green.

Further, contrary to the Examiner's assertion, Luthra actually does not appear to Applicants to specifically concern compositions for disinfecting a surface. Rather, Luthra's invention concerns chemically modified polymeric materials and medical devices fabricated or coated with these material. *See, e.g.*, abstract and claims 1 and 7. Thus, while Luthra teaches

polymeric materials (*i.e.*, compounds), it does not appear to disclose *compositions* of its polymers with other agents for coating a surface. Applicants invite the Examiner to cite to any information concerning compositions for coating medical devices in Luthra that include a chemically-modified polymer of Luthra and other agents.

As to Luthra, Applicants note that the Examiner cites to column and line number citations in Luthra. Luthra, however, is a published PCT application and is not set forth in a column format. Therefore, Applicants are unclear regarding the Examiner's support for her statements and request clarification.

(2) **Even if Luthra Taught Application of a Composition Comprising Chlorhexidine to Coat a Medical Device, There Would Nevertheless Be No *Prima facie* Case of Obviousness Because Pelerin Teaches Chelator Compositions, Which Falls Outside of the Scope of the Instant Claims**

Applicants vigorously assert that one of ordinary skill in the art would not be motivated to coat a medical device with a composition that includes chlorhexidine and a dye based on the evidence of record. In the sections below, Applicants present further detailed argument in support of their position. Assuming *arguendo* that one of ordinary skill in the art combined Pelerin and Luthra, there would nevertheless be no *prima facie* case of obviousness because one of ordinary skill in the art would likely have included a chelator in the coating composition since Pelerin teaches that presence of a chelator in its compositions is of crucial importance. *See, e.g.*, abstract and para [0004] – [0006]. As discussed above, the presently pending claims concern methods of disinfection that involve application of a composition *consisting essentially of* chlorhexidine and a dye that is gentian violet or brilliant green. Thus, as written the claims exclude additional ingredients that materially affect the basic and novel properties of the claimed invention. As discussed above, the present application teaches that chelators (such as trisodium

n-(2-hydroxyethyl)ethylenediaminetriacetate; [GV[†]HEDTA]) materially affect the basic and novel properties of the invention. Therefore, given that any motivation to combine teachings of Pelerin with Luthra would likely result in inclusion of a chelator agent in the coating composition, such a method would fall outside of the scope of the presently claimed invention.

(3) **One of Ordinary Skill in the Art Would Not Find Motivation in Pelerin to Incorporate a Dye into the Polymeric Composition of Luthra**

One of ordinary skill in the art would not be motivated to incorporated a dye into the chemically modified polymer compositions of Luthra based on the teachings of Pelerin. As discussed above, Pelerin concerns dental restoration solutions for root or dentinal tubule treatment that include an orally compatible solvent and a chelating agent at a pH of between 1.2 and 4. See abstract. The solutions of Pelerin are thus aqueous solutions; Pelerin specifically teaches that the chelating agent is dissolved in water. See para [0006]. Pelerin teaches that "[a] dye is optionally present to identify a tooth region contacted with the inventive solution." Para [0012]. One of the dyes set forth is gentian violet. When applied to a root or dentinal tubule, one of ordinary skill in the art would expect that the aqueous solution of Pelerin would not be permanently applied to the root or dentinal tubule, but instead could be washed off such as by rinsing. Pelerin teaches that "a solution of the present invention is typically dabbed or dropped onto a specific site on a tooth for a limited period of time." Para [0013]. Absence of the dye would generally thus indicate absence of the solution from the root or dentinal tubule. One of ordinary skill in the art would not find an indicator dye to be of benefit in the coating compositions of Luthra because the coatings of Luthra are not intended to be temporary coatings that are washed off of a surface, but instead are polymeric materials that are actually fabricated into the device or coated onto the surface of a device. There would be no need to indicate

presence or absence of the polymer because the device itself is necessarily composed of the polymeric material. Nothing would be gained by incorporating an indicator dye into the polymeric compositions of Luthra given that the device itself is composed of the polymeric material of Luthra.

(4) **No Reasonable Expectation of Success**

There would be no reasonable expectation of success based on Pelerin and Luthra for one of ordinary skill in the art to chemically modify the polymers of Luthra to include a moiety that is an indicator dye. Examples 12-18 of Luthra (page 25, line 9 – page 29, line 19) provides detail concerning chemical synthesis of polymeric compounds that include chemical linkage of a biguanide to a polymer. The Examiner has not provided any information to indicate that one of ordinary skill in the art would be able to include a dye in the reaction mixture without disrupting the formation of the polymer itself or the binding of the biguanide to the polymer. The reaction to incorporate biguanide into a polymer occurs in organic media, under anhydrous conditions. Applicants do not identify any teaching or suggestion in either Luthra or Pelerin to suggest that an indicator dye can be incorporated into the reaction mixture with a reasonable expectation that doing so would not disrupt the synthesis of the polymeric compounds of Luthra. Applicants do not identify any information in either reference to suggest that a dye would remain stable under the stringent reaction conditions of Luthra such that it could continue to function as a dye, or whether the dye would become chemically attached to the polymer, or whether the dye would degrade when exposed to the anhydrous reaction conditions set forth in Luthra. Applicants invite the Examiner to comment further.

There would also be no reasonable expectation of success based on Pelerin and Luthra for one of ordinary skill in the art to coat polymeric devices of Luthra with a composition that

includes a dye and chlorhexidine. Luthra concerns a method that involves chemically reacting a biguanide with a polymer such that the biguanide becomes linked to the polymer. If the dye is used as an indicator of the chemically modified polymer of Luthra, then presumably it would have to either be chemically bonded to the polymer or to the biguanide. There is no guidance in either reference to indicate how such a reaction may be achieved. The Examiner is invited to comment in this regard. It is also noted that the *preferred devices* of Luthra are *contact lenses and intra-ocular lenses*. See page 7, lines 29-30. Incorporation of dye into the lenses may disrupt lens clarity and interfere with physical properties of the lenses, a topic which has not been addressed by the Examiner. As to catheters, the Examiner has failed to consider whether incorporation of gentian violet in polymeric material for fabrication of devices would interfere with physical properties or stability of the device. Applicants do not identify any information in Luthra that suggests that incorporation of compounds such as dyes can be successfully incorporated into a polymer matrix without disrupting the polymer matrix. One finds no reasonable expectation of success in Pelerin, which teaches inclusion of dyes in aqueous solutions and not polymer matrices. Therefore, in the absence of a reasonable expectation of success that a dye can be successfully incorporated into the polymers of Luthra, there can be no *prima facie* case of obviousness.

b. The Prior Art Cited by the Examiner Does Not Render the Claims Obvious Because It Does Not Include Detailed Enabling Methodology

The Federal Circuit has observed that "an obviousness finding was appropriate where the prior art 'contained ***detailed enabling methodology*** for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful.'" *In re Kubin*, 561 F.3d 1351, 1359-1360 (Fed. Cir. 2009), citing to *In re*

O'Farrell, 853 F.2d 894, 902 (Fed. Cir. 1988) (emphasis added). In the instant case, the Examiner's position further falls short because she has not demonstrated that Luthra combined with Pelerin provide a detailed enabling methodology. It is unclear how one of ordinary skill in the art would incorporate a dye into the polymeric materials of Luthra. No information is provided which would enable one of ordinary skill in the art to determine how one might bind a dye to the chemically modified polymers of Luthra without an undue amount of experimentation, nor has any evidence been cited to suggest that any such polymers would be suitable for fabrication of medical devices. Further, even if one of ordinary skill in the art somehow admixed a dye and a chemically modified polymer of Luthra, there is no evidence from the cited references suggesting these mixtures would be suitable for fabrication or coating of medical devices or that they would retain infection control properties. For example, would inclusion of a dye in a mixture of polymers inhibit polymerization of the material such that the material would not longer be suitable for its intended purpose? Would one of ordinary skill in the art be able to chemically attach a biguanide to a polymer if gentian violet was included in the reaction mixture? The Examiner has not addressed any of these issues. It would require undue experimentation for one of ordinary skill in the art to attempt to make such determinations. Therefore, given that the cited references fail to provide an enabling methodology, there can be no *prima facie* case of obviousness.

c. Applicants' Evidence of Surprising and Unexpected Results is Sufficient to Rebut an Obviousness Challenge

(1) The Examiner's Citation of *In re Rau* is Not Dispositive

In the final Office Action, the Examiner, citing *In re Rau*, asserts that "it is well settled that a patent cannot be granted for an applicant's discovery of a result, even though it may be unexpectedly good, which would flow logically from the teaching of the prior art." *In re Rau*,

253 F.2d 437, 117 USPQ 215 (CCPA 1958). As an initial matter, Applicants note that the Examiner, by making this comment on the record, appears to concede that the present invention is unexpectedly good.

Applicants next point out that their results do not flow logically from the teaching of the prior art. As discussed above, one of ordinary skill in the art would not be motivated to modify a composition of chemically-modified polymers for fabricating medical devices to include a dye based on a reference which teaches a particular dye in an aqueous dental restoration solution. How one of ordinary skill in the art might attempt to incorporate a dye is unclear. For example, does the examiner expect that one of ordinary skill in the art would covalently attach a dye moiety to the polymer moiety or to the biguanide moiety? There is no information in either Pelerin or Luthra to provide any reasonable expectation that this can be accomplished. Does the Examiner expect that the indicator dye of Pelerin would simply be admixed with the polymer of Luthra? No information has been cited in either reference to suggest that a dye could reasonably be expected to be incorporated into Luthra's polymer without disrupting polymerization or compromising the integrity of the medical device. Thus, the Examiner's position that combining a dye with the chemically-modified polymers of Luthra would flow logically from the teachings of the prior art is untenable.

Further, *In re Rau* does not concern obviousness but instead addresses anticipation. Regarding *In re Rau*, it is an appeal from the decision of the Board of Appeals of the Patent Office affirming the rejection by the primary examiner of all claims in appellant's application for a patent on a power transmission device. *In re Rau*, 253 F.2d at 438. The sole issue before the court was whether appellant's claims were anticipated by two prior art references. *In re Rau*, 253 F.2d at 439. A single feature was relied on as distinguishing each of the claims on appeal

from the prior art. *In re Rau*, 253 F.2d at 438-439. It is specifically set forth that "[i]f that feature involves patentable novelty, all of the appealed claims are allowable; if not, all of them were properly rejected." *Id.* The court then proceeded to analyze the prior art, concluding that the prior art disclosed appellant's invention. The appellant had submitted an affidavit of record to provide evidence of exceptionally good results, arguing that the references do not suggest that such exceptional results would have been obtained. *Id.* It is in this context that the court commented that "a patent cannot be granted for an applicant's discovery of a result, even though it may be unexpectedly good, which would flow logically from the teaching of the prior art." *In re Rau*, 253 F.2d at 440. Thus, *In re Rau* stands for the proposition that evidence of unexpectedly good results does not overcome a rejection based on ***anticipation, not obviousness***. The court did not address obviousness, and thus no conclusion can be drawn based on *In re Rau* that surprising and unexpected results cannot overcome a *prima facie* case of obviousness.

(2) ***Agrizap v. Woodstream* Does Not Support the Examiner's Position that Surprising and Unexpected Results Can Overcome a *Prima facie* Case of Obviousness**

Applicants now turn to a case cited by the Examiner during the telephonic interview – *Agrizap v. Woodstream*, 520 F.3d 1337, 86 USPQ2d 1110 (Fed. Cir. 2008). The Examiner indicated during the telephonic interview that this case may stand for the proposition that surprising and unexpected results cannot overcome a *prima facie* case of obviousness. Applicants disagree. Agrizap sued Woodstream for fraudulent misrepresentation and for infringement of Agrizap's patent directed to an electronic rat trap in district court. *Agrizap*, 520 F.3d at 1339. The district court confirmed in part and reversed in part, and the parties filed cross appeals. *Id.* One issue addressed by the Federal Circuit was whether the patent claims were obvious based on a prior art rat trap and prior art patents. *Agrizap*, 520 F.3d at 1341. The Court

considered Agrizap's objective evidence of nonobviousness, including the commercial success of an embodiment, copying by Woodstream, and long felt need in the market for electronic rat traps. The court, following consideration of the evidence, found the evidence insufficient to overcome the Woodstream's *prima facie* case of obviousness. *Agrizap*, 520 F.3d at 1344. The only difference between the claimed invention and the prior art rat trap was the type of switch used to complete the circuit. *Id.*

This case does not support the present Examiner's position that secondary considerations cannot be used to overcome a *prima facie* case of obviousness. No evidence of surprising and unexpected results were set forth in Agrizap. Therefore, *Agrizap v. Woodstream* does not support the Examiner's position that surprising and unexpected results may not be used to overcome a *prima facie* case of obviousness.

Further, the court did consider the secondary indicia rather than disregard them. Under the facts of *Agrizap* that evidence was not sufficient to overcome Woodstream's *prima facie* case of obviousness. Thus, this case does not stand for the proposition that secondary indicia of obviousness cannot rebut a *prima facie* case of obviousness.

(3) **The Manual of Patent Examining Procedure and Case Law Supports Applicants' Position that Surprising and Unexpected Results Can Overcome a *Prima facie* Case of Obviousness**

MPEP §716.02(a) includes a section entitled "Greater than Expected Results are Evidence of Nonobviousness." This section of the *MPEP* specifically indicates that "[e]vidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (*i.e.*, demonstrating 'synergism')." *MPEP* §716.02(a) citing *Merck & Co. Inc. v Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843

(Fed. Cir.), cert. denied, 493 U.S. 975 (1989). It is further noted that "a greater than additive effect is not necessarily sufficient to overcome a *prima facie* case of obviousness because such an effect can either be expected or unexpected" and that applicants "must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage." *MPEP* §716.02(a) citing *Ex parte The NutraSweet Co.*, 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991). Thus, the *MPEP* provides specific guidance to Examiners concerning the determination of whether surprising and unexpected results can overcome a *prima facie* case of obviousness.

In the instant case, Applicants have demonstrated that chlorhexidine in combination with gentian violet or brilliant green has superior disinfecting capabilities, with synergistic results (*i.e.*, disinfecting capability greater than either chlorhexidine alone or brilliant green alone). Further, there is no evidence in the prior art to suggest that such a synergistic result would have been expected. Still further, the synergistic disinfecting capability of the combination of chlorhexidine and dye (gentian violet or brilliant green) is of a significant, practical advantage. For example, coating of catheters and other devices may help reduce the incidence of hospital-acquired infections, as discussed in the specification. Therefore, Applicants have demonstrated surprising and unexpected results in accordance with the requirements of the *MPEP* in a manner sufficient to overcome a *prima facie* case of obviousness.

(4) **Recent Case Law Indicates that a *Prima facie* Case of Obviousness Can Be Overcome By Surprising and Unexpected Results**

Recent case law supports the concept that evidence of surprising and unexpected results may be found to be sufficient to overcome a *prima facie* case of obviousness. In *KSR International Co. v. Teleflex Inc.*, it is noted that the U.S. Supreme court left open the door for

surprising and unexpected results to overcome a *prima facie* case of obviousness by providing that §103 bars patentability unless "the improvement is more than the predictable use of prior art elements according to their established functions." *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007) (emphasis added). The Federal Circuit has recently opined that "[i]f a patent challenger makes a *prima facie* showing of obviousness, the owner may rebut based on 'unexpected results' by demonstrating 'that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising and unexpected." *The Procter & Gamble Company v. Teva Pharmaceuticals USA, Inc.*, 2009 WL 1313321 (Fed. Cir., May 13, 2009), citing *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). Thus, case law makes it clear that surprising and unexpected results can be rebutted by evidence of surprising and unexpected results.

(5) **Applicants' Evidence of Surprising and Unexpected Results is Extensive and Sufficient to Overcome a *Prima facie* Case of Obviousness**

Even if the Examiner argues that a *prima facie* case of obviousness has been made, which Applicants as discussed above assert is not the case, Applicants would nevertheless overcome such a *prima facie* case of obviousness because Applicants' methods are surprisingly and unexpectedly superior compared to methods using either dye alone or basic reagent alone. This evidence has been set forth in Applicants' response to the previous Office Action, and for the sake of completeness it is summarized below.

(a) Evidence in the Specification

As Applicants have previously set forth in their response to the Office Action dated August 21, 2007, the Example section of the specification provides strong evidence of synergy of the combination of a dye and a basic reagent. The combination has broad-spectrum activity

against various nosocomial microorganisms, including resistant bacteria and fungi. *See, e.g.*, specification, page 9, lines 18-27. Table 2 and Table 3 on page 20 of the referenced patent application show zones of inhibition (ZOI) produced by coated endotracheal PVC tubes (using DCM or MeOh). As set forth in the application on page 20, lines 16-19, "endotracheal PVC tubes impregnated with Gendine (GN) are far more effective against all organisms when compared with those impregnated with CHX, and more effective than PVC tubes impregnated with GV against *Pseudomonas aeruginosa.*"

Table 4 on page 21 of the referenced application shows ZOI produced by coated silicone catheters. Page 21, lines 10-12 states that "data in Table 4 shows how silicone catheters impregnated with GN are more effective in inhibiting *MRSA*, *PS* and *C. parapsilosis* than catheters impregnated with either GV or CHX."

Table 5, on page 21 of the present application, shows ZOI produced by coated polyurethane catheters (PU). Page 21, lines 24-27 states that "PU catheters impregnated with GN are more effective than PU catheter impregnated with GV in inhibiting *Pseudomonas aeruginosa*, and more effective than PU catheters impregnated with CHX against all three organisms, *MRSA*, PS and *C. parapsilosis*." Applicants specifically point out this evidence to the Examiner, who has questioned whether Applicants have demonstrated surprising and unexpected results of the combination of Gentian violet and chlorhexidine for a polyurethane device.

Table 6, on page 22 of the present application, shows ZOI produced by coated silk sutures. Page 21, lines 10-12 provides that "silk sutures coated or impregnated with GN are significantly more effective in inhibiting *MRSA*, *PS* and *C. parapsilosis* than sutures coated with either GV or CHX."

Similarly, Tables 7-10 on pages 24-25 show similar synergy against various bacterial and fungal organisms, when GV was combined with other basic reagents on the surfaces of medical devices.

(b) Declaration of Dr. Raad filed with Response to Office Action dated Jan. 11, 2006

Furthermore, as set forth in the Declaration of one of the inventors, Dr. Issam Raad (filed with the response to the Office Action dated January 11, 2006; "the Raad declaration"), additional evidence was provided demonstrating that the combination of a basic reagent and a dye has antiseptic ability as a mouthwash, coating of a glove, or coating of a catheter than is more than additive compared to either dye alone or basic reagent alone. Applicants particularly point out this evidence to the Examiner, who has questioned whether Applicants have set forth surprising and unexpected results concerning the combination of chlorhexidine and brilliant green. The information set forth in this declaration supports the statement in the specification that the present invention concerns novel antiseptic compositions with broad-spectrum activity against various nosocomial microorganisms, including resistant bacteria and fungi and the specific recitation of brilliant green in the specification. *See, e.g.*, abstract, page 4, lines 16-19, page 9, lines 18-27 and page 10, lines 20-29.

Pages 1-3 of Exhibit 1 of the Raad declaration describes studies reporting the antiseptic efficacy of gloves coated with various combinations of a dye and a basic reagent. The antiseptic efficacy of gardine, a solution of brilliant green dye and chlorhexidine, prepared in various solvents was studied, as set forth on page 1 of Exhibit 1 of the Raad declaration. The results indicate that all compositions that included a dye and basic reagent showed excellent efficacy as an antiseptic coating of gloves, with zones of inhibition being comparable with no leaching.

The antiseptic efficacy of compositions of brilliant green dye and chlorhexidine (gardine) as an antiseptic mouthwash was also assessed. Exhibit 1, page 4 of the Raad declaration. The results showed that while brilliant green dye or chlorhexidine alone had MINIMAL OR NO effect as an antiseptic, a combined solution of the two was extremely effective as an antiseptic, as there was more than an additive effect in killing bacteria and yeast compared to either agent alone. In another study, it was shown that gardine is an excellent antiseptic alcohol free mouthwash, with an antiseptic efficacy comparable to three well-known mouthwashes. Exhibit 1, page 4.

Studies were also conducted to assess the antiseptic efficacy of central venous catheters coated with chlorhexidine in combination with one of the selected dye from a group of Erythrosin B, Sudan III, Fast Green, Brilliant Green, Solvent Green 3, Quinoline Yellow, Indigo Carmine, Gentian violet and Tartrazine. Exhibit 1, pages 6-8. The results show that the combination of chlorhexidine and each of the dyes was extremely effective as an antiseptic coating, and that antiseptic efficacy was more than additive compared to either dye or chlorhexidine alone. Exhibit 1, pages 6-8.

(c) Second Declaration of Dr. Raad

In addition, the second Declaration of Dr. Issam Raad ("the Second Declaration; Exhibit A of the response to the Office Action dated July 25, 2006), sets forth a summary of data from his laboratory that further demonstrates a high level of synergy of the combination of a basic reagent and a dye in antiseptic ability. Second Declaration, ¶8 and Exhibit 1 of Second Declaration.

Dr. Raad notes that the most serious forms of catheter related bloodstream infections are those caused by fungi, particularly Candida albicans. Second Declaration, ¶9. This is the infection with the highest mortality rate – around 40%. *Id.* His laboratory team found that

gendine (GV and CHX) mixed in a specific molar ratio to coat catheters and devices provides unexpectedly superior synergy against Candida albicans. *Id.* The strain used in the studies summarized in Exhibit 1 was obtained from a patient who suffered from catheter-related fungemia/candidemia caused by Candida albicans (strain 009-3072). *Id.* In the first part of the study summarized in Exhibit 1, they calculated a minimal inhibitor concentration (MIC) and minimal fungicidal concentration (MBC) for each of the components, GV and CHX. The MIC/MBC was 0.5 microgram per mL for the GV and 16 microgram per mL for CHX. *Id.*

Dr. Raad's group then tested for synergy of the combination of CHX and GV over a range of 1:1 to 100:1, and obtained the results described on page 2 of Exhibit 1. Second Declaration, ¶10. Boxes that are shaded had a complete kill of the Candida albicans at the respective concentrations of the components that are lower that the MIC and MBC of CHX alone and GV alone. *Id.* The best synergistic data was obtained at a ratio of CHX:GV of 1:1 and 10:1, with a plateauing effect at 25:1 and thereafter. *Id.* In other words, Dr. Raad's team found that there is synergy obtained at 50:1 and 100:1 but it is not appreciably different from 25:1. *Id.*

As noted by Dr. Raad, these results clearly establish that the claimed methods using a combination of a dye and basic reagent are surprisingly and unexpectedly superior compared to methods of disinfecting using dye alone or basic reagent alone. Second Declaration, ¶11.

Further, Dr. Raad's group has published a study (Exhibit 2 of response to Office Action dated August 21, 2007) that demonstrates that mouthwash compositions that have a ratio of dye:basic reagent of 10:1-66:1 demonstrated synergistic antimicrobial efficacy against free-floating and biofilm forms of Candida albicans. Second Declaration, ¶12.

The Examiner argues in the Office Action that the data in the specification and the information set forth in the Declarations of Dr. Raad are insufficient to demonstrate a synergistic

effect of the claimed methods. In response to this assertion, Applicants have previously submitted the Declaration of Dr. Ray Hachem, (Exhibit B of response to Office Action dated August 21, 2007). Dr. Hachem is a skilled expert in infectious disease therapy and control. Hachem Declaration, ¶3. Dr. Hachem was asked whether the results set forth in the present patent application and the information set forth in the first and second Declarations of Dr. Raad demonstrate that the presently claimed invention demonstrates a synergistic antiseptic effect compared to dye alone or basic reagent alone. Hachem Declaration, ¶5. Dr. Hachem has cited to a definition of "synergy" from the 2007 instructions to authors from the journal entitled "Antimicrobial Agents and Chemotherapy." Hachem Declaration, ¶6. In paragraph 6 of his declaration, Dr. Hachem cites to specific sections of the patent application and evidence from the declarations of Dr. Raad which demonstrate synergy. He concludes that the results set forth in the specification and the data cited in the Raad declarations clearly establishes that compositions that include a dye and basic reagent in the molar ratios set forth in the claims exhibit surprising and unexpected synergy for disinfecting and/or sterilizing surfaces or a fluid compared to dye alone or basic reagent alone. Hachem Declaration, ¶8.

(d) Third Declaration of Dr. Raad

As further evidence of the surprising and unexpected superior results of the claimed methods, Applicants herein submit the third declaration of Dr. Issam Raad (Exhibit B, "Third Declaration"). Dr. Raad is one of the inventors of the present application. He has attached as Exhibit 1 of his declaration a summary of results of studies which demonstrate the synergism between gentian violet and chlorhexidine, and between brilliant green and chlorhexidine. Third Declaration, ¶2. Table 1 and Table 2 demonstrate the results for a mouthwash solution which includes brilliant green and chlorhexidine, and Table 3 shows the results for silicone catheter segments coated with a composition that includes gentian violet and chlorhexidine. *Id.*

The results provided by Dr. Raad in Table 1 show lack of antiseptic activity produced by each of brilliant green and chlorhexidine when each was tested alone, in the concentrations shown in the table. Third Declaration, ¶3, citing to Exhibit 1. However when brilliant green and chlorhexidine were used together, in those same concentrations, the solution was able to completely inhibit the growth of *Klebsiella pneumoniae*, MRSA, and *Candida albicans*. *Id.* A solution that includes 0.004 mg/ml brilliant green and 0.006% chlorhexidine corresponds to a molar ratio of 22:1 brilliant green:chlorhexidine. A solution that includes 0.008 mg/ml brilliant green and 0.006% chlorhexidine corresponds to a molar ratio of 44:1 brilliant green:chlorhexidine. A solution that includes 0.008 mg/ml brilliant green and 0.012% chlorhexidine corresponds to a molar ratio of 22:1 brilliant green:chlorhexidine. The results in Table 1 indicate that there is synergism between brilliant green and chlorhexidine. *Id.*

The results in Table 2 show lack of antiseptic activity produced by each of brilliant green and chlorhexidine when each was tested alone, in the concentrations shown in the Table. Third Declaration, ¶4, citing to Exhibit 1. However when brilliant green and chlorhexidine were used together, in those same concentrations, the solution was able to completely inhibit the growth of *Candida albicans*. *Id.* A solution that includes 0.008 mg/ml brilliant green and 0.012% chlorhexidine corresponds to a molar ratio of 22:1 brilliant green:chlorhexidine. A solution that includes 0.008 mg/ml brilliant green and 0.024% chlorhexidine corresponds to a molar ratio of 11:1 brilliant green:chlorhexidine. The results in Table 2 indicate that there is synergism between brilliant green and chlorhexidine. *Id.*

The results in Table 3 show that silicone catheter segments coated with a solution that includes gentian violet and chlorhexidine produced zones of inhibition, against Methicillin resistant *Staphylococcus aureus* (MRSA), while segments coated with either gentian violet alone

or chlorhexidine alone failed to produce any zones of inhibition. Third Declaration, ¶5, citing to Exhibit 1. Zones of inhibition indicate absence of bacterial growth within that zone. The results in row 1 correspond to a molar ratio of 2.6:1 of chlorhexidine:gentian violet. The results in row 2 correspond to a molar ratio of 1.6:1 of chlorhexidine:gentian violet. The results in Table 3 indicate that there is synergism between gentian violet and chlorhexidine. *Id.*

This unexpected high level synergy whereby either agent alone has no effect (zones of inhibition of zero) and the combination results in sizable zones of inhibition has been demonstrated in various experiments presented in the patent application (see, *e.g.*, Tables 2, 3, 4, 6, 8 and 10). For example, neither gentian violet or chlorhexidine had any activity or zones of inhibition against *Pseudomonas aeruginosa* (PS4025) on the surfaces of endotracheal tubes, silicone catheters and silk sutures as shown in Tables 2, 3, 4 and 6, pages 8-9 of the patent application, whereas the combination (gendine) had large zones of inhibition. Similar results are shown on Tables 8 and 10 on page 10 for gentian violet with other basic agents, such as chloroxylenol or chlofoctol against other bacteria (*Alcaligenes faecalis*) or fungi (*C. parapsilosis*) that often cause serious infections in hospitalized patients.

In *KSR International Co. v. Teleflex Inc.*, the Supreme Court stated that when an obvious modification "leads to the anticipated success," the invention is likely the product of ordinary skill and is obvious under 35 *KSR Int'l co. v. Teleflex inc., 550 U.S. 398,* 127 S.Ct. 1727,1742 (2007). As discussed above, the modification is not obvious. Further, the Examiner has not set forth any information that that establishes that binding a dye to a chemically modified polymer of Luthra or admixing a dye with the chemically modified polymer of Luthra would lead to the surprising and unexpected results that Applicants have observed. Given that at the very least it is

unclear whether combining a dye with a polymeric material of Luthra would be suitable as a disinfecting agent, there can be no *prima facie* case of obviousness.

In view of the foregoing evidence and arguments, to the extent that the Examiner might have set forth any *prima facie* case of obviousness, it has been successfully overcome.

2. Claims 97, 120, and 123 Are Not Unpatentable Based on Luthra and Perelin, and Further in View of Ibsen

Claims 97, 120, and 123 are rejected under 35 U.S.C. §103(a) as being unpatentable over Luthra and Pelerin as applied above, and further in view of Ibsen *et al.* (U.S. Patent 4,204,978; hereinafter "Ibsen"). The Examiner argues that Luthra and Pelerin render obvious the claimed methods as to the composition of chlorhexidine and gentian violet. The Examiner adds Ibsen as allegedly disclosing the equivalence of brilliant green (malachite green) and gentian violet as dye indicators, concluding that it would be *prima facie* obvious for one of ordinary skill in the art to lead to the claimed invention. Applicants respectfully traverse.

For the reasons discussed above, the discussion of which is incorporated into this section, Luthra in view of Pelerin fails to render the claimed methods obvious. Furthermore, Ibsen fails to remedy the deficiencies of Luthra and Pelerin. Ibsen is cited by the Examiner has disclosing brilliant green as an indicator dye. Ibsen concerns aqueous compositions that include a dye, a surfactant, and an acid as a tooth crack detector for use during dental procedures. Example 4 (col. 4, lines 66-68) discloses 0.3% solution of malachite green in an aqueous mixture of water, glacial acetic acid, and dioxyl sodium sulfosuccinate. The arguments set forth above as to Pelerin apply similarly to Ibsen with the exception of the argument concerning chelators (Ibsen does not appear to disclose a chelator as a required ingredient in its compositions). Nevertheless, for each of the foregoing reasons, there would be no *prima facie* case of obviousness. Further, to the extent that the Examiner might have set forth a *prima facie* case of obviousness, it has been

successfully rebutted by Applicants' evidence of surprising and unexpected results concerning methods employing the combination of chlorhexidine and brilliant green as set forth previously.

For each of the foregoing reasons, it is respectfully requested that the rejection of claims 97, 120, and 123 under 35 U.S.C. §103(a) be withdrawn.

3. Claims 98 and 100 are Not Unpatentable Based on Perelin in View of Ibsen

Claims 98 and 100 are rejected under 35 U.S.C. §103(a) as being unpatentable over Pelerin in view of Ibsen. Claim 100 has been canceled without prejudice or disclaimer as discussed above. Therefore, only claim 98 is at issue in this rejection.

Claim 98 is directed to a method for disinfecting and/or sterilizing a floor, a table-top, a counter-top, hospital equipment, a wheel chair, or a medical device comprising applying a composition consisting essentially of chlorhexidine and brilliant green to the floor, table-top, counter-top, hospital equipment, wheel chair, or medical device, wherein the molar ratio of chlorhexidine:brilliant green in the composition is 1:1 to 25:1.

As discussed above, Pelerin is cited as disclosing the use of gentian violet in a chlorhexidine-containing disinfecting composition to indicate to the user where the composition has been applied. The Examiner further cites Pelerin as teaching that the composition is "typically dabbed or dropped" onto the specific site; that the dental art typically uses swabs and/or gauze for dabbing and a droppers (a medical device) for dropping, and that the contact of the composition of Pelerin would intrinsically meet the claim limitation of disinfecting a medical device. Ibsen is cited by the Examiner as allegedly disclosing the equivalence of brilliant (malachite) green and gentian violet as dye indicators in dental compositions, and that it would have been obvious to one of ordinary skill in the art to substitute the brilliant green of Ibsence for

the gentian violet of Pelerin as the results would have been expected. Applicants respectfully traverse the rejection of claim 98.

One of ordinary skill in the art would be motivated to include a chelator in the coating composition since Pelerin teaches that presence of a chelator in its compositions is of crucial importance as discussed above. *See, e.g.*, abstract and para [0004] – [0006]. The presently pending claims concern methods of disinfecting that involve application of a composition *consisting essentially of* chlorhexidine and brilliant green. Thus, the claim language excludes additional ingredients that materially affect the basic and novel properties of the claimed invention. As discussed above, the present application teaches that chelators (such as trisodium n-(2-hydroxyethyl)ethylenediaminetriacetate; [GV[†]HEDTA]) materially affect the basic and novel properties of the invention. Therefore, given that any motivation to combine teachings of Pelerin with Ibsen would result in inclusion of a chelator agent in the coating composition, such a method would fall outside of the scope of the presently claimed invention.

For each of the foregoing reasons, it is respectfully requested that the rejection of claim 98 under 35 U.S.C. §103(a) be withdrawn.

E. <u>New Claims</u>

New claims 135-137 have been added. New claims 135 and 136 depend from claim 69, and new claim 137 depends from claim 136. Support for the new claims can be found generally throughout the specification, such as in the claims as originally filed and in the following sections of the specification: page 4, lines 15 – page 14, line 4. The new claims are not obvious for the reasons set forth above concerning independent claim 69.

F. Conclusion

In view of the foregoing, it is respectfully submitted that each of the pending claims is not obvious under 35 U.S.C. §103(a) and in condition for allowance, and a Notice of Allowance is earnestly solicited. The Examiner is invited to contact the undersigned attorney at (512) 536-5639 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

Monica A. De La Paz
Reg. No. 54,662
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
512.474.5201 (telephone)
512.536.4598 (fax)

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